

## ANIMAL MODEL OF HUMAN DISEASE

# *Alimentary Toxic Aleukia (Septic Angina, Endemic Panmyelotoxicosis, Alimentary Hemorrhagic Aleukia)*

## *T-2 Toxin-Induced Intoxication of Cats*

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### Biologic Features

Alimentary toxic aleukia (ATA), a frequently fatal mycotoxicosis, follows the ingestion of overwintered grain or grain by-products infested with fungi, and primarily affects poor rural families in the USSR.<sup>1,2</sup> ATA in man is characterized by leukopenia, agranulocytosis, necrotic angina, a hemorrhagic rash, sepsis, exhaustion of the bone marrow, bleeding from the nose, throat, and gums, and fever.<sup>3,4</sup> The toxic metabolites of fusarial species have been intensively studied in efforts to establish the specific etiology of ATA.<sup>5-11</sup> Studies with rats, mice, guinea pigs, rabbits, dogs, swine, sheep, poultry, cattle, and horses were unsuccessful in the search for an animal model.<sup>4</sup>

The syndrome of ATA has been induced in cats by administration of the sesquiterpene T-2 toxin (3 $\alpha$ -hydroxy-4 $\beta$ , 15-diacetoxy-8 $\alpha$ -[3-methylbutyrolaxy] 12, 13-epoxytrichothec-9-ene), a naturally occurring trichothecene isolated from *Fusarium sporotrichioides*.<sup>12,13</sup> T-2 toxin in gelatin capsules, administered every 48 hours *per os* to healthy cats (dosage: 0.08 mg/kg body weight), regularly resulted in a fatal disease (average survival time: 3 weeks) with symptoms of generalized lassitude, weakness, bloody feces, hind-leg ataxia, conjunctivitis, and vomiting. In the terminal stages, anorexia, dyspnea and paralysis were noted, while dehydration and weight loss (average 22%) were more severe.

Gross postmortem findings included severe emaciation, enlarged and hemorrhagic lymph nodes, hemorrhages of the gastric and intestinal mucosa,

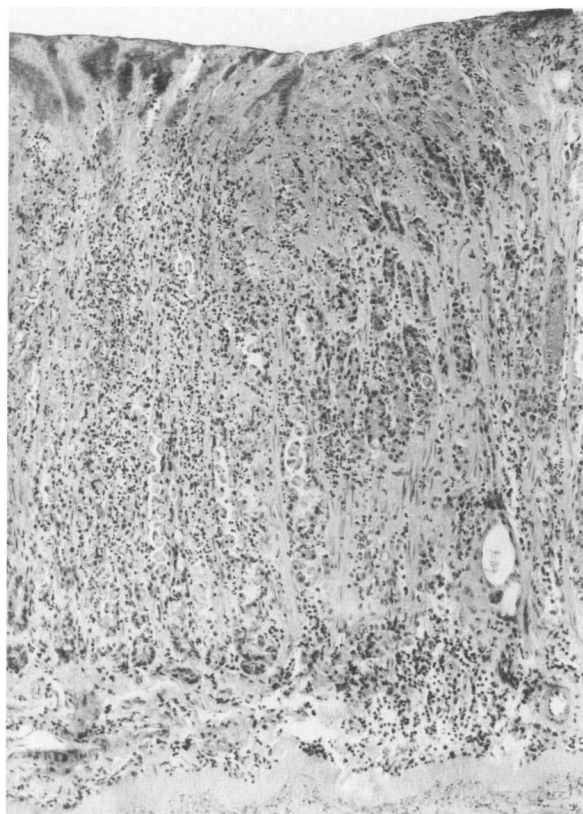
lung congestion, petechiae and ecchymoses of the myocardium, and subcutaneous hemorrhages.

Microscopic observations of the alimentary tract showed erosion of the gastric epithelium, frequently with bacterial invasion and cryptitis (Figure 1); necrosis of intestinal villi and deep glandular epithelium; erythrocytic aggregations in capillaries of the villi. Additional histologic findings included: hyperemia of the subcapsular and medullary sinuses of all lymph nodes; hemosiderosis in the spleen, lung, and lymph nodes; and pulmonary congestion and edema of the lungs. In the spleen depletion of lymphocytes from the germinal centers was evident; desquamation of the sinus epithelium was pronounced (Figure 2); and marked erythrophagocytosis reflected the irritation of the reticuloendothelium. Bone sections, reflecting severe damage to hematopoiesis, showed hemorrhagic marrow, hypocellularity, numerous multinucleated giant cells throughout the stroma (Figure 3), fibrinoid material in the sinusoids, and large vacuoles reflecting fatty changes.

A generalized decrease in circulating blood cells with anemia, leukopenia, and thrombocytopenia was a constant hematologic finding in all cats intoxicated with T-2 toxin. A slight initial leukocytosis was followed by a severe progressive leukopenia. Neutro-

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**Figure 1**—Gastric epithelium (fundus) of cat, after 14 doses of T-2 toxin, showing surface erosion, ulcerative cryptitis, and invasion of the mucosa by bacterial colonies. (H&E,  $\times 100$ )

phils were enlarged and showed bizarre nuclear patterns and blue foamy cytoplasm; erythrocyte changes included anisocytosis, macrocytosis, and polychromatism; and thrombocytes showed unusual forms, eg, giant platelets. During intoxication, packed cell volume and hemoglobin concentration were reduced, while the erythrocyte sedimentation rate was greatly elevated. Prolonged bleeding time and whole blood coagulation time reflected defective hemostasis.

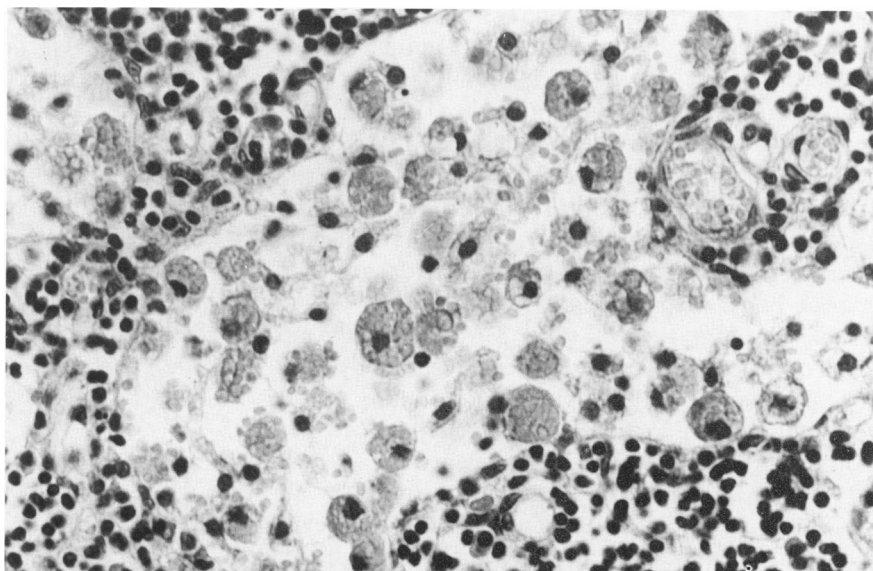
### Comparison With Human Disease

ATA in man initially includes inflammation of the gastric and intestinal mucosa, a severe progressive leukopenia, anemia, and an increased erythrocyte sedimentation rate. Subsequently petechial hemorrhages of both the skin and mucosa together with enlarged lymph nodes are seen. Pancytopenic abnormalities intensify, and blood coagulation is diminished. The pathologic features of the respiratory system include bronchopneumonia, pulmonary hemorrhages, sepsis, and lung abscesses. Vomiting, bloody feces, lassitude, and incoordination are also observed. All of the clinical features, the pancytopenia, and the gross and microscopic pathologic changes seen in cats receiving T-2 toxin via the alimentary route were strikingly similar to the disease syndrome of alimentary toxic aleukia in man.<sup>1,3-5</sup>

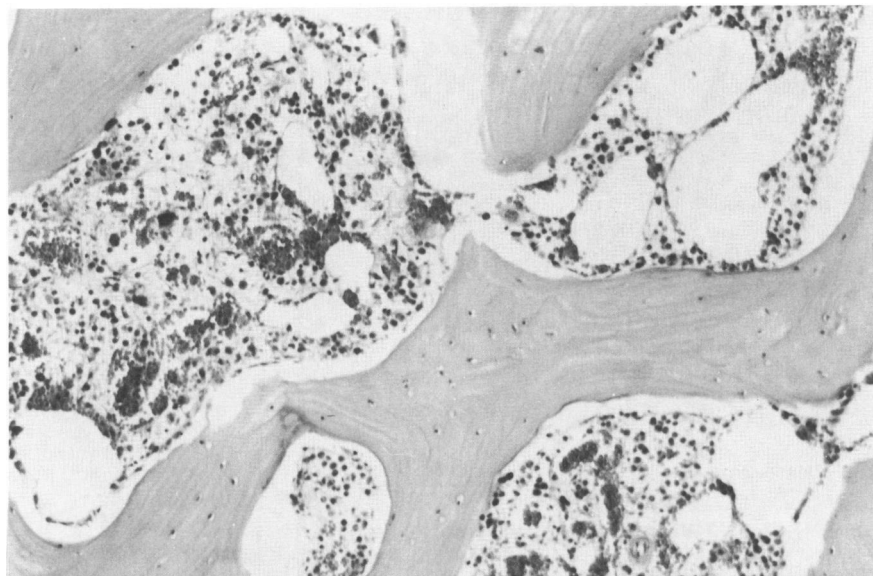
### Usefulness of the Model

This feline model provides for greater insight into

**Figure 2**—Section of spleen from cat, after 14 doses of T-2 toxin, showing depletion of lymphocytes, desquamation of the sinus endothelium, and marked erythrophagocytosis. (H&E,  $\times 500$ )



**Figure 3**—Section of sternal bone from cat after 20 doses of T-2 toxin, showing hypoplasia of the marrow and many multinucleate giant cells scattered throughout the stroma; sinusoidal congestion is pronounced. (H&E,  $\times 400$ )



the pathogenesis, therapy, and immune features<sup>14</sup> of mycotoxicoses generally, and trichothecene-induced disease specifically. The model allows for study of the effects of long-term trichothecene ingestion; provides for detection of early mycotoxic changes before irreversible effects occur; can aid in improving techniques for identification and measurement of mycotoxins in tissues, body fluids, and excreta; and enables the study of trichothecenes 1) as inhibitors of protein synthesis and 2) in carcinogenesis. The cat is a laboratory animal large enough for evaluating the pharmacologic, pathologic, hematologic, biochemical, immunologic, and clinical aspects of alimentary toxic aleukia and analogous disease.

#### Availability

T-2 toxin is produced by Makor Chemicals Ltd., P.O. Box 6570, Jerusalem, Israel. Cats remain readily available laboratory animals, whose general good health and immunity to feline panleukopenia should be established prior to their use in ATA studies.

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